Combined expression of KLK4, KLK5, KLK6, and KLK7 by ovarian cancer cells leads to decreased adhesion and paclitaxel-induced chemoresistance.

Chemoresistance is a critical feature of advanced ovarian cancer with only 30% of patients surviving longer than 5 years. We have previously shown that four kallikrein-related (KLK) peptidases, KLK4, KLK5, KLK6 and KLK7 (KLK4-7), are implicated in peritoneal invasion and tumour growth, but underlying mechanisms were not identified. We also reported that KLK7 overexpression confers chemoresistance to paclitaxel, and cell survival via integrins. In this study, we further explored the functional consequences of overexpression of all four KLKs (KLK4-7) simultaneously in the ovarian cancer cell line, OV-MZ-6, and its impact on integrin expression and signalling, cell adhesion and survival as contributors to chemoresistance and metastatic progression. Quantitative gene and protein expression analyses, confocal microscopy, cell adhesion and chemosensitivity assays were performed. Expression of ?5?1/?v?3 integrins was downregulated upon combined stable KLK4-7 overexpression in OV-MZ-6 cells. Accordingly, the adhesion of these cells to vitronectin and fibronectin, the extracellular matrix binding proteins of ?5?1/?v?3 integrins and two predominant proteins of the peritoneal matrix, was decreased. KLK4-7-transfected cells were more resistant to paclitaxel (10-100 nmol/L: 38-54%), but not to carboplatin, which was associated with decreased
apoptotic stimuli. However, the KLK4-7-induced paclitaxel resistance was not blocked by the MEK1/2 inhibitor, U0126. This study demonstrates that combined KLK4-7 expression by ovarian cancer cells promotes reduced integrin expression with consequently less cell-matrix attachment, and insensitivity to paclitaxel mediated by complex integrin and MAPK independent interactions, indicative of a malignant phenotype and disease progression suggesting a role for these KLKs in this process.